APPENDIX D
DOSE-RESPONSE ASSESSMENTS

This appendix presents dose-response assessments for drycleaning (perchloroethylene and hydrocarbon solvents) and for machine wetcleaning chemicals.

D.1 DRYCLEANING

This section presents dose-response assessments for perchloroethylene (PCE) and hydrocarbon (HC) solvents (specifically, Stoddard solvent).

D.1.1 Perchloroethylene

Cancer

A specific cancer dose-response assessment is developed under the assumption that an agent is a human carcinogen. The dose-response assessment is intended to quantitatively define the relationship between the dose of the agent and the likelihood of a carcinogenic effect. First, an attempt is made to predict the relationship from epidemiologic studies. In the case of PCE, the epidemiology is insufficient to define the relationship.

Turning to the animal data, hepatocellular adenomas and carcinomas were produced in PCE-exposed mice of both sexes (NTP, 1986) and mononuclear cell leukemia and kidney tumors were seen in male and female rats (NTP, 1986). As discussed in the hazard assessment, the mechanisms by which PCE induces these endpoints are not clearly understood. More than one mechanism has been proposed by which PCE might cause each of these responses; the available data do not clearly support any of the various mechanistic views. The leukemia and liver responses in rodents suggest a general, accelerating influence on underlying neoplastic processes. The kidney tumors in male rats might be associated with the toxic effects of PCE in the kidney and/or with mutagenic activity of a secondary (mutagenic) metabolite of PCE, dichloro-vinyl cysteine; the data do not reveal an answer. As a whole, the data do not point to the linearity at low doses generally expected of mutagenic compounds, although the elevated responses in high background tumors could suggest an activity that builds on background processes. This would give the appearance of linearity at doses producing responses close to background rates, regardless of mutagenic activity.

Although the data are not strongly linear, they are also not strong enough to describe how PCE might have a threshold or a non-linear dose-response relationship at low doses, nor do they assist in building an alternative model for response in that range. Consequently, the Cleaner Technologies Substitutes Assessment presents two assessments of dose response: one uses a procedure that assumes linearity at low doses; the second a procedure that stops short of projecting response to low doses and examines the extent to which anticipated exposures differ from study levels (sometimes called margins of exposure or MOEs) to characterize human risk. This latter utilizes a quantity called the ED_{10} (see explanation below).

This section uses several existing analyses, supplemented by analyses along the philosophy of the recent proposed revision (USEPA, 1996) of USEPA's Carcinogen Risk Assessment Guidelines (USEPA, 1986b). Both approaches use the animal data in hand (NTP, 1986) and rely on analyses carried out and published in the Addendum to the Health Assessment Document (USEPA, 1986a). These analyses first examined the data in the experimental range. Following the approach used in the Addendum, exposure concentrations for the experimental animals were transformed to human equivalent metabolized dose.[1] Owing to the date of the Addendum's analyses, these equivalents are based on a species proportionality with $(\text{body weight})^{2/3}$.[2]

The CTSA uses human equivalent metabolized doses with the mouse and rat tumor responses to establish predicted dose-response relationships in the range of the experiment. The tumor prevalence data are the same as in USEPA (1986a) but the slope factor is not, since USEPA (1986a) averaged results from six data sets using a geometric mean. To avoid double counting animals with adenomas and carcinomas, the mouse carcinoma-only data sets have been omitted for this assessment. Thus, the analyses are based on incidence of male and female mouse liver adenomas and/or carcinomas and male and female rat mononuclear cell leukemia by taking the geometric mean of the unit risks of the four individually modeled species-sex combinations.[3]

The first step in establishing a predicted relationship is to fit a model to the data. As mentioned at the outset of this section, data are insufficient to support an agent-specific model reflecting a presumed mode of action. In the range of observation, most quantal models used for curve-fitting will be equivalent and USEPA used a so-called multistage model in its earlier analyses (USEPA, 1986a; USEPA, 1991).[4]

Linear-at-Low-Doses Approach

Linear-at-low-doses approaches address the range in which excess risk is expected to be at most 1%. Historically, USEPA has estimated an upper bound for low-dose risk by incorporating an appropriate linear term into the statistical bound to the multistage curve. At sufficiently small exposures, any higher-order terms in the polynomial will contribute negligibly, and the graph of the upper bound will look like a straight line. That gives a unit risk that can be multiplied by exposures to estimate upper bounds on excess

[1]This transformation represented a direct transformation from a human study with urinary metabolized dose. The Addendum also presents results based on crude use of a four-compartment model, with no allowance for variability or uncertainty. Subsequent work in the literature (e.g., Hattis et al., 1986; Chen and Blancato, 1987; Bois et al., 1996) has expanded the horizons for transformation and incorporation of variability and uncertainty.

[2]USEPA is considering the use of an alternate factor, proportional with $(\text{body weight})^{3/4}$ (USEPA, 1992) but has not yet adopted it (although it was proposed in USEPA [1996]). Because many technology options and scenarios as well as several dose-response relationships will be considered in the PCE risk characterization, this alternate factor has not been applied here. Its effect on comparisons is expected to be less than half an order of magnitude.

[3]That is, the geometric mean of female and male mouse liver adenomas and carcinomas and female and male rat mononuclear cell leukemia. An alternate view could consider the female results corroboratively or in conjunction with the more sensitive male results within species. As an example, despite the higher background rate in male mice that contributes to differences in response shapes, the results are within an order of magnitude for the two sexes.

[4]This is an exponential model approaching 100 percent risk at high doses with a shape at low doses described by a polynomial function.

lifetime cancer risk for specific scenarios. This "linear-at-low-doses" unit risk would be 7.1×10^{-7} per $\mu g/m^3$ of PCE in air. This unit risk should not be used for lifetime average daily exposures greater than 1.4×10^4 $\mu g/m^3$ (risk of 1%). (These values may be compared to the unit risk of 5.78×10^{-7} per $\mu g/m^3$ of PCE in air and its corresponding use ceiling of 1.7×10^4 $\mu g/m^3$ from the double-counting calculations in USEPA [1986a], Table 4-6.)

Nonprojection Approach

The method that does not project response to low doses or exposures relies on an ED_{10}, or the dose associated with an estimated excess tumor response in 10% of an experimental group. A multistage model (here, a two-stage model, or exponential with quadratic argument model, as used in the linear-at-low-doses approach) is used to obtain the ED_{10}. Response rates below this percentage are beyond the resolution of most experiments, and the various possible model shapes that might have been fitted to the data begin to diverge.

In addition to the ED_{10}, a lower bound on that 10%-response-dose is calculated to provide a sense of some of the properties of the experiment(s)/studies from which risk is characterized. Because the PCE modeling used units of human equivalent metabolized doses, the ED_{10} and its lower bound are divided by 7.83×10^{-6} mg/(body weight)$^{2/3}$/day[5] to obtain units of the inhaled concentration ($\mu g/m^3$, human exposure) equivalents (details in USEPA, 1986a). The ED_{10} is 2.7×10^5 $\mu g/m^3$; the lower bound on the ED_{10} is 1.4×10^5 $\mu g/m^3$. These figures are compared to projected exposures to assess the MOE ratios as described in Chapter 5. A recent proposal (USEPA, 1996) would take a straight line from the response at the ED_{10} to the background response.[6] There is still discussion about this proposed approach and it has not been adopted for this assessment.[7]

Effects Other Than Cancer

Non-cancer effects vary widely in the characteristics of their manifestation. To provide a common vocabulary for comparing substances, regardless of the effect that may be of most concern, a value called the Reference Dose (RfD; for ingested or dermally applied substances) or Reference Concentration (RfC; for inhaled substances) is derived. The standard approach to the RfD/RfC calls for the identification of the spectrum of effects associated with a given chemical, typically giving primary attention to a "critical effect" exhibiting the lowest No-Observed-(Adverse-)Effect Level (NOAEL or, since this is really an experiment-related term, its conceptual equivalent from epidemiology, studies of humans). Effects are identified using "principal studies," which "are those that contribute most significantly to the qualitative assessment of whether or not a particular chemical is potentially a systemic toxicant in humans. In addition, they may be used in the quantitative dose-response assessment phase of the risk assessment" (IRIS, 1998).

[5]This is the estimated amount metabolized over a 24-hour period when an individual is exposed to 1 $\mu g/m^3$ continuously.

[6]Whether a line is drawn to background from the ED_{10} or a "linearized" upper bound on a multistage model is utilized, the estimated risks are presumed to be upper bounds on risks owing to the way a straight line will include most S-shaped curves.

[7]The ED_{10}-line would give a unit risk of 3.7×10^{-7} per $\mu g/m^3$; its bound would give 6.9×10^{-7} per $\mu g/m^3$. These differ by approximately less than one order of magnitude from the "linearized multistage procedure" result.

An RfD for PCE is published in IRIS (1998). A value of 0.01 mg/kg/day, in which there is medium confidence, is based on the critical effect, hepatotoxicity in mice, from a study by Buben and O'Flaherty (1985). The NOAEL for this effect is corroborated by weight gain in rats at the same level in a study (Hayes et al., 1986) where rats lost weight at higher doses.

For the CTSA, USEPA has derived a provisional RfC of 0.17 mg/m^3, in which there is medium confidence, based on the critical effect, mild renal tubule damage, as reported in Franchini et al. (1983). This RfC is provisional because it was derived by a single USEPA program office with limited cross-office review. Vu (1997) describes the derivation in standard USEPA format.

The RfD/RfC is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD/RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure without an appreciable risk of deleterious effects during a lifetime. RFDs/RfCs can be derived for the non-carcinogenic health effects of compounds that are also carcinogens.

Discussion of Principal and Supporting Studies

Detailed discussion of the data contributing to derivation of the RfD appears in IRIS (1998). All the studies available for derivation were carried out in animals. Buben and O'Flaherty (1985) exposed Swiss-Cox mice to PCE in corn oil by gavage at six doses (20, 100, 200, 500, 1,000 or 1,500 mg/kg) and control, 5 days/week for 6 weeks. The NOAEL from this study was 20 mg/kg/day or 14 mg/kg/day when adjusted for continuous exposure. Hayes et al. (1986) also established 14 mg/kg/day as a NOAEL. Administered PCE in drinking water, the group of Sprague-Dawley rats receiving the least of three positive doses (14, 400, or 1,400 mg/kg/day) showed no difference from the control group.

The CTSA has identified Franchini et al. (1983), Lauwerys et al. (1983), and Solet and Robins (1991) as the principal studies for the RfC. These studies have been carried out in drycleaning workers. The basis for the RfC is (Franchini et al., 1983), a cross-sectional study carried out across four exposure venues relating to organic solvents, including 57 workers exposed to PCE in 29 drycleaning shops. Their average exposure time was 13.9 years (standard deviation 9.8). The exposure intensity was assessed by measuring the end-shift excretion of trichloroacetic acid (TCA). The study authors converted the mean TCA level for the group to a breathing-zone, time-weighted average (TWA) of about 10 ppm (PCE) in air. Renal function impairment indicators (four types of urinalysis outcome) were compared between these subjects and control subjects selected to be biologically and socially similar, but unexposed. Controls were drawn from factories associated with the other three exposure types (painters/benzene in metal working, styrene workers, workers exposed to short-chain alkanes) and considered as two reference groups, one predominantly female, one predominantly male.

The subjects showed mean values of lysozymuria and urinary β-glucuronidase significantly elevated above both reference groups. This testing was carried out by a statistical method that may have identified sources of group differences incorrectly. The authors suggested that increased urinary β-glucuronidase might be related to a faster cellular turnover in tubular epithelium due to a mild toxic effect, whereas lysozymuria might be a marker of more definite lesions throughout the renal tubules. Thus the level of 10 ppm is considered as a Lowest-Observed-Adverse-Effect-Level (LOAEL) equivalent.

The Lauwerys et al. (1983) study is also cross-sectional, including 26 drycleaning workers (24 female) who had been exposed to PCE over a 6-year period in six shops. Certain urinary enzymatic levels were measured, albeit not the same ones as Franchini et al. (1983), as were certain plasma enzymatic levels. Three psychomotor tests were administered. No differences were attributed by the investigators to exposure to PCE. Average exposure was approximately 20 ppm PCE.

Solet and Robins (1991) studied 197 drycleaning workers and found no evidence of adverse effects on renal function, as measured by levels of urinary protein, albumin, and n-acetyl-glucosaminidase (NAG). They did not look at urinary β-glucuronidase. These workers were exposed to a mean PCE concentration of 14 ppm. No control group was studied; thus, the investigators concentrated their effort on modeling the variability among exposed individuals.

Derivation of RfD

The steps to derive the RfD from the principal study include: (1) selecting a critical effect, (2) identifying the highest level consistent with the resolution of the study at which that effect is not seen or the level at which that effect first appears, taking possible confounding factors into account, (3) associating a measure of exposure with that level, and (4) applying scientific judgment to select uncertainty factors (UFs). If the measure of exposure is not an applied or potential dose for the individual, some relationship between that measure and applied/potential dose is needed.

USEPA's RfD/RfC Workgroup carried out these steps, which are reflected in the IRIS (1998) discussion of uncertainty and modifying factors, additional comments, and confidence pertaining to the RfD. Uncertainty factors were incorporated reflecting intraspecies variability, interspecies variability, and inference from a subchronic (6-week) study to chronic exposures. Although confidence in the Buben and O'Flaherty (1985) study was low, owing to incomplete histopathology at the NOAEL, no single study had the necessary combination of desirable characteristics for derivation; confidence in the database as a whole was medium, contributing to a medium confidence in the RfD.

Derivation of Provisional RfC

The steps to derive the RfC from the principal study include the same four as for the RfD: (1) selecting a critical effect, (2) identifying the highest level consistent with the resolution of the study at which that effect is not seen or the level at which that effect first appears, taking possible confounding factors into account, (3) associating a measure of exposure with that level, and (4) applying scientific judgment to select UFs. Again, if the measure of exposure is not an applied or potential dose for the individual, some relationship between that measure and applied/potential dose is needed. For an RfC, however, internal dosimetric considerations may be related to several classes of inhaled substances.

For PCE, the study from which a critical effect was selected was Franchini et al. (1983), and that effect is mild renal tubule damage. It was reported to have been seen at exposures as low as 10 ppm (in air, TWA over work-shift) based on authors' calculations from TCA. The reported derived average level of 10 ppm is equivalent to 70 mg/m^3; this is a LOAEL-equivalent for this study. Adjustment to continuous exposure, assuming no dose rate effects, involves averaging the duration of occupational exposure (40 hours) over the 168 hours in a week, and gives an adjusted daily exposure of 17 mg/m^3. Because this is an occupational study, a 10-fold factor is applied to account for sensitive individuals, and a factor of 10 is

applied in order to use a LOAEL as a NOAEL. For use in the CTSA in an occupational setting, only the factor of 10 to adjust a LOAEL to a NOAEL was used.

Additional Comments/Studies for the RfC

Another human study provided a possible explanation for some of the differences among the three principal studies, concerning the appropriate metric of PCE exposure for the RfC. Stewart et al. (1981) studied volunteers exposed 5 days/week for 1 month to PCE concentrations of 20, 100, and 150 ppm. Their subjects were mostly sedentary during exposure except for brief periods of exercise, presumably less active than if they had been exposed occupationally. Based largely on one individual's observed exercise experience and post-activity measurements, the study authors concluded that TWA concentrations may not reflect an individual's true body burden from PCE exposure. The apparent discordance among the three principal studies may be partly due to different approaches to estimating cross-sectional PCE exposure, as well as to misclassification of exposure due to a lack of direct measurements of historical exposure.

The Stewart et al. study could be used to estimate an approximate RfC. The study, however, is especially small. Individuals served as their own control subjects in an experimental context, where volunteers were exposed for a varied number of hours. The study authors stated that exposure to 100 ppm PCE led to major changes in electroencephalogram results of three of four male subjects and four of five female subjects, and that the altered EEG pattern was similar to that seen in healthy adults during drowsiness, light sleep, and the first stages of anesthesia. Application of the same uncertainty factors as above, for using a LOAEL as a NOAEL and to account for sensitive individuals, as well as an uncertainty factor to allow for chronic exposure, leads to an RfC lower than using the Franchini et al. study. By the study authors' arguments, however, this TWA of 100 ppm reflects a lower PCE body burden than would be expected of workers exposed at 100 ppm, suggesting a further adjustment would be necessary.

Use of the TWA of 10 ppm from the Franchini et al. study requires assuming that the TWA represents the typical range of exposures the subjects experienced. If the TWA had been higher than 10 ppm in earlier years of the subjects' exposures, and this higher TWA were more causally linked to the increase in urinary enzymes than the TWA measured in the study, then the RfC here would be overly protective. On the other hand, because no measure of variability in exposure concentrations is available, the UF adjustment for sensitive populations may be an insufficient reflection of the range of human response. No additional UF was applied for extension to lifetime exposure; the inhaled PCE exposures are unlikely to accumulate indefinitely to produce this endpoint, the duration of exposure of 13.9 years with a standard deviation of 9.8 years applied to the mean age of 43 (standard deviation 9.1) covers a substantial part of the subjects' adult lives, and the modifying factor is less than the variability in the derived exposure.

Several more recent studies (Altmann et al., 1990, 1992, 1995; Ferroni et al., 1992; Cavalleri et al., 1994) have examined neurobehavioral endpoints. These have included cognitive deficits, deficits in visual evoked potentials and visual acuity, and prolonged reaction times. Difficulties in using these studies for deriving a provisional RfC include an experimental setting in which the control group was exposed at 10 ppm (the derived mean level at which effects were seen in Franchini et al., 1983) or occupational exposures at means above 10 ppm, large standard deviations on reported exposure levels, and poor association of the exposure levels with the effects. The New York State Department of Health (NYSDOH, 1997) used a collection of studies including these and several others together with its own methods to

derive several endpoint-specific criteria for evaluating non-carcinogenic effects for adults and children. Its possible adult values range from 0.28 mg/m^3 to 0.36 mg/m^3, with an overall recommendation that the criterion for ambient air be 0.1 mg/m^3. This value is consistent with the above derived provisional RfC.

Animal data support the endpoint choice and conclusions from human data. NTP (1986) reported renal and hepatic effects, including tumors, in rodents exposed by inhalation for 2 years to high levels of PCE (100 and 200 ppm in mice, and 200 and 400 ppm in rats). It reported that 100 ppm (approximately 700 mg/m^3), the lowest concentration tested, was a LOAEL for mice. Exposure to 100 to 1,600 ppm for 6 hours/day, 5 days/week, for 13 weeks was associated with hepatic and renal effects; a concentration of 1,600 ppm was fatal to 20-70% of rats and mice and was associated with reduced body weights. Exposure of rats to 0, 200, or 400 ppm, and of mice to 0, 100, or 200 ppm for 2 years was associated with a dose-related decrease in survival in male rats and both sexes of mice. Long-term exposure to PCE was associated with leukemia in rats at 100 and 200 ppm and in rats at 200 and 400 ppm, karyomegaly (in rats of both sexes), and hyperplasia in renal tubular cells (in male rats). No tumors of the respiratory tract were reported. A NOAEL was not established by this study. Although the appearance of increased mortality at 100 ppm in male mice could suggest this as a Frank Effect Level (FEL), this increase was not in evidence until after 74 weeks.

Discussion of Confidence in the RfC

PCE has been studied for a variety of endpoints, and human and animal studies are available relating to systemic toxicity and reproductive and developmental effects. The animal literature is extensive; the human literature has gaps. On balance the database is of medium quality. This RfC is based on humans, exposed in a most typical setting. The Franchini et al. (1983) study does not permit a quantitative dose-response relationship to be derived and does not characterize the variability of the exposure concentrations. Thus, some lower exposures may still demonstrate effects, and the Solet and Robins (1991) study, lacking a control group, cannot be used to establish a NOAEL in lieu of the Franchini et al. (1983) LOAEL. A rough calculation of an RfC from Stewart (1981), based on a neurotoxicity outcome, is slightly lower than the RfC derived from Franchini et al. (1983), based on renal function, suggesting the magnitude is reasonable. An RfC based on the (animal) NTP (1986) study without any dose conversions would be of the same order of magnitude (based on a LOAEL of 100 ppm, or approximately 125 mg/m^3 for continuous exposure, and applying an uncertainty factor and a modifying factor of 1,000 and 1, respectively).

D.1.2 Hydrocarbon Solvents

No oral RfD, inhalation RfC, cancer unit risk, or slope factor has been established to date for Stoddard solvent or any other hydrocarbon solvent. ATSDR (1995) determined that it did not have human or animal studies suitable for developing what it calls Minimum Risk Levels, which resemble RfD/RfCs, for intermediate- or chronic-duration exposures to Stoddard solvent in air.

For purposes of the CTSA, a non-cancer comparison value has been derived from Carpenter et al. (1975a, 1975b). As discussed for PCE, the standard approach to the RfD/RfC calls for the identification of the spectrum of effects associated with a given chemical, with primary attention given typically to a "critical effect" exhibiting the lowest NOAEL (or, since this is really an experiment-related term, its conceptual equivalent from epidemiology, studies of humans). Effects are identified using "principal

studies," which "are those that contribute most significantly to the qualitative assessment of whether or not a particular chemical is potentially a systemic toxicant in humans."

The spectrum of effects that has been associated with Stoddard solvent is described in Chapter 3 and Appendix C. Because the human observations provide poor exposure information when occupationally based and are at relatively high levels when experimental, a comparison value was selected from the animal literature. Rather than develop a provisional level for the CTSA without critical review, a level was chosen directly from a study. A 13-week study (Carpenter et al., 1975a, 1975b) in dogs showed no statistically significant clinical and histopathological differences as low as 480 mg/m^3 (84 ppm) and as high as 1,900 mg/m^3 (330 ppm). Because a parallel study in male rats showed kidney tubular regeneration at both 1,100 mg/m^3 (190 ppm) and 1,900 mg/m^3 (330 ppm), but none at 480 mg/m^3 (84 ppm), 480 mg/m^3 is identified as a NOAEL, with the recognition that it is from a subchronic study.

D.2 MACHINE WETCLEANING CHEMICALS

No oral RfD, inhalation RfC, cancer unit risk, or slope factor has been established to date for any of the sample machine wetcleaning chemicals reviewed for the CTSA, and their data do not provide the necessary information to derive provisional levels for the CTSA. This makes quantitative assessment of their risks moot. Nonetheless, the principles in quantitative considerations of mixtures are pertinent to their qualitative assessment.

Under ideal circumstances, information would be available for the mixture or formulation as a whole. More typically, information is available on the ingredients (components) or on just some of them (in this case, on none). Often, certain components are exchangeable, with selection based on their function in the process, but with exposure and toxicity properties unique to the selection. In Section 3.3, some information on examples of these selections was provided for the wetcleaning process. Many of the aqueous-based ingredients have, themselves, been tested in mixtures that may resemble the formulations for use in machine wetcleaning. Such tests are helpful to the extent that the tested mixture is known and resembles the expected wetcleaning formulation. Details of the tested formulations, unfortunately, were not available for most of the components described in the CTSA.

Quantitative assessment of mixtures using their components in the absence of specific interaction information would typically rely on an assumption that the components produce their toxicities independently; information on ways one or more components may modify others is incorporated qualitatively. Mixtures with just a few ingredients may be characterized quantitatively and qualitatively more readily than mixtures with many dissimilar ingredients.

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